REMARKS

Claims 1 and 7 have been amended to clarify that exchanging acyltransferase domains either by restriction enzyme or by *in vivo* recombination results in a change in the nature of the extender unit substrate accepted by the encoded PKS. Support for this amendment is found, for example, on page 7, at lines 18-21. The further clarifying limitation that the extender unit specificity of the involved PKS be different is imported from dependent claims 6 and 14 into claims 1 and 7, respectively. Accordingly, claims 6 and 14 are canceled.

In addition, claims 15-30 have been canceled as directed to a non-elected invention. Entry of the amendment is respectfully requested.

The invention takes advantage of the modular nature of the various regions of the PKS and the interchangeability of acyltransferase regions with different substrate specificities for extender units.

The Rejections Under 35 U.S.C. § 112, Paragraph 1

All claims were rejected as assertedly enabled only for the exchange of AT domains between rapamycin and erythromycin-related PKS. The rationale for this rejection is that, at the time the grandparent application was filed – *i.e.*, 30 April 1997, only rapamycin and erythromycin sequences were available in the art. However, the invention is not directed to compositions of matter dependent on the sequence of any newly isolated and purified and sequenced PKS. The invention is directed to a technique which is applicable to any modular PKS once it becomes available. Since the invention is directed to a method which is applicable generically, it is enabled and can be performed as described just as soon as the relevant sequences become available.

No matter how many nucleic acid sequences encoding modular PKS are available at any given time, additional PKS sequences will become available as the years pass. There is clearly no question that performance of such a generic method on any of the subsequently elucidated sequences would be covered by the scope of the claim to the method *per se*. Clearly the Office would not take the position that a claim to a method for exchanging AT domains would not be infringed by performing such a method on a newly discovered and sequenced nucleic acid encoding a PKS. In symmetry with this concept, there is no reason to expect that applicants be required to supply, in support of the claim, the structures of all PKS that exist. It is sufficient to demonstrate that the method of the invention works with those sequences currently available, since there is no reason to doubt that the method would be equally applicable to subsequently discovered and sequenced nucleic acids.

Accordingly, the rejection for lack of enablement under 35 U.S.C. § 112, paragraph 1, may properly be withdrawn.

The Art Rejections

Anticipation

Claims 1-14 were rejected as assertedly anticipated under § 102(b) by Katz (WO 93/13663) or under § 102(e) by Katz (U.S. patent 5,824,513) and by Katz (U.S. patent 6,200,813). The disclosures of the first two documents are substantially identical. The '813, as a continuation-in-part, has additional disclosure as compared to the PCT '663 publication and the '513 patent.

Taking these documents in turn, applicants are unable to find in the '663 publication any description of exchange of AT domains in the relevant encoding nucleic acids. In order for anticipation to be found, each and every element of the claim must be found explicitly or inherently

in a single prior art document. The Office does not cite any description in '663 of substituting an AT region of one PKS-encoding nucleic acid for that of another. The section on page 2, referred to by the Office, describes alterations of a first nucleic acid by excising portions thereof, mutating them, and reintroducing the mutated portions. It does not describe excising any portion of a nucleic acid encoding a first PKS and using it to replace an excised portion of a nucleic acid encoding a second PKS, much less referring to the AT region specifically.

The Office is correct that the sequence and identification of modules of the erythromycin PKS are shown in Figures 1 and 2, but this does not constitute an anticipation of the method of the invention. The section on page 6, at lines 26-29, says only that the correct enantiomer of methylmalonyl CoA in the extender unit is specified by the AT function of erythromycin. It does not say, as stated by the Office, that the extender unit employed at each condensation is specified by the AT function. In any event, this does not amount to a disclosure of the method of the invention either. The Examiner is correct, of course, that page 4 recognizes that a multiplicity of nucleic acids encoding PKS are available from various organisms, but this section does not describe the method of the invention. And if the enablement rejection above is based on the unavailability of these sequences, the '663 document is not enabled in this respect either.

The Office then refers to page 7, lines 12-18, which simply state that "[t]ype III changes will result in the biosynthesis of macrolide rings of length reduced (deletion) or increased (insertion) by two carbon units or macrolide rings altered in specific portions of the chain (replacement)." There is no mention of restriction enzymes (a requirement of claims 1-5) or any mention of *in vivo* recombination in this section. Further, there is nothing describing a method in which an AT region

specifically will be replaced by a different AT region. Type III changes are simply defined in terms of their results on page 5, lines 35, *et seq*.

Furthermore, none of Examples 7, 11, 15, 19 or 24 describe AT region replacements. Example 7 simply results in a deletion of 813 base pairs in the KR5 region; Example 11 describes manipulations which result in the deletion of a 102 base pair fragment from KR2; Example 15 describes transfer of a 487 base pair deletion created in a DH4 region to another vector; Example 19 describes the transfer of a delete in the KS1 region from one plasmid to another; and Example 24 describes the transfer of a KS2 deleted region into another vector. There is no mention in any of these examples of an AT transfer and no mention of the use of restriction enzymes, as required by claims 1-5.

Claim 16 in '663 which does at least describe manipulation of AT, depends from claim 1, which describes a method for *altering* a *single* PKS-encoding gene, not substituting a region of a first PKS-encoding DNA in place of an excised region of a second PKS-encoding DNA. Claim 1 describes a process quite different from that of the present invention wherein a portion of only a "first" PKS encoding DNA is excised, mutated, and replaced. Thus, claim 16 does not anticipate the method of the invention which requires a first PKS-encoding DNA and a second PKS-encoding DNA. Applicants are unsure as to the referent of "(1-3, 7, 8, 10 and 14)." Neither examples of these numbers nor claims of these numbers appear relevant.

As to the concluding statement that '663 teaches that the method is applicable to any gene cluster, referring to claims 4-7 and 11-13, no mention of the strains listed appears in these claims; mention does appear on page 36, at lines 10-20, but, again, the method described in '663 involves only a single PKS-encoding nucleic acid, not two.

Since there is no teaching of all of the elements claimed in claims 1-14 by '663, this document cannot anticipate the claims.

The Examiner is correct that the '513 document is the same disclosure as '663 and so the foregoing comments apply equally to this document. No anticipation can be found based on this document either.

Turning, now, to the '813 patent, which is a continuation-in-part of '513, any new matter in this patent has an application date subsequent to the application date of the grandparent application herein, which grandparent is identical to the present specification. The Office asserts that claims 1-10 of '813, which involve isolating first and second DNA segments comprising modular PKS and exchanging the AT portions, are fully supported by '513. No basis is provided for this conclusion. Applicants find nothing in the '513 patent which supports these claims, and if such portions exist, applicants believe it is the obligation of the Office to indicate the location of such disclosure in the specification of '513. Examples 1-3 and 9-10, cited by the Office as supportive of claims 1-10 of '813, are not present in the '513 patent. All the support for claims 1-10 appears to have been added to the application filed 23 December 1997. Accordingly, the '813 patent is not properly citable as a prior art document.

In any case, no section of the '813 patent has been noted which could anticipate the subject matter of claims 1-5, which require the use of a restriction enzyme-based procedure to make the replacement.

For the reasons set forth above, it is believed that all rejections based on anticipation of claims 1-5 and 7-13 remaining in the case may be withdrawn.

Obviousness

Only claims 7-14 were rejected under 35 U.S.C. § 103. Accordingly, claims 1-5 are now free of the art entirely. With regard to claims 7-14, the disclosure of Katz' '663 is combined with that of U.S. patent 4,713,337.

First, applicants again point out that '663 never suggests replacement of an AT region from a first PKS-encoding nucleic acid into a corresponding deleted region of a second PKS-encoding nucleic acid. The method suggested by '663 for manipulating a modular PKS is to excise a region of that PKS, mutate it, and then put it back. Therefore, unless the secondary document remedies this defect, it cannot suggest the present invention as now claimed. There is no assertion that the secondary document does make this suggestion, and indeed it does not. On this basis alone, the rejection should be withdrawn.

With regard to the disclosure of '337, this patent discloses gene deletion by homologous recombination. Homologous recombination is the technique employed in claims 7-13 herein, but this is a standard well-recognized technique, disclosed, as a matter of fact, by '663. There is no suggestion, however, to apply this technique to the method of the present invention. The process in which this is applied in '337 is to convert cells from RecA+ to Reca-. There is no suggestion in '337 to apply this standard technique to anything else.

For this reason, the rejection of claims 7-14 for obviousness may be withdrawn.

Again, applicants note that there is no outstanding rejection for obviousness over prior art of claims 1-5.

Double-Patenting

Claims 1-14 were rejected as assertedly double-patenting over claims 1-6 of U.S. patent 6,391,594. A terminal disclaimer is included to obviate this rejection.

Conclusion

The rejection for asserted lack of enablement may be withdrawn as the claims are drawn to a method to manipulate modular polyketide synthase-encoding nucleic acids, regardless of what they are. There should be no necessity to disclose the sequences of all possible PKS-encoding DNA's, known and unknown, in order to support a method that is shown applicable to any and all of them.

The rejection for anticipation over the art may be withdrawn with regard to claims 1-5 in part because no prior art document describes manipulating PKS-encoding DNA by the use of excision and replacement employing restriction enzymes.

None of the pending claims, claims 1-5 and 7-13, are anticipated by any of the two documents properly cited as prior art, as these documents describe only manipulating a single nucleic acid encoding a modular PKS by removing portions, mutating them, and replacing them. The '813 patent, which does describe the method of the invention, has an application date subsequent to that to which the present application is entitled. Although the Office asserts that the relevant claims in '813 are supported by one of the earlier documents, no evidence for this support has been adduced.

Accordingly, applicants believe claims 1-5 and 7-13 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any

required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 300622000508.

Respectfully submitted,

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